

**REMARKS/ARGUMENTS**

**I. Status of the Claims**

Claims 1-50 were originally filed in this application. Claims 1-50 were subject to a Restriction Requirement. After election of claims, Claims 1-12, 14-17, 20-28 and 33-37 are examined on the merits. The Examiner has withdrawn claims 24 and 26-27. Applicants traverse the withdrawal of claims 24 and 26-27. Claims 1-12, 14-17, 20-28 and 33-37 have been rejected. Applicants have canceled claims 3, 14-17, 20, 28 and 33. Applicants have amended claims 1-2, 5-12, 18, 21, 26-27, 29-32, 34-37, 42, 44, 47 and 48. Applicants have incorporated Formula (Ia), which is a species of Formula (I), into claims 1-2 and 34-37. New claims 51-64 have been added. New claims 51-62 are directed to species of Formulae (Ib) and (Ic) and are readable on the elected species. New claims 63 and 64 are directed to Formulae II and III. The amendments are fully supported by the specification and no new matter is added.

**II. The Invention**

The present invention provides a method of modulating an Edg-1 receptor mediated biological activity in a cell by contacting a cell expressing the Edg-1 receptor with an amount of a non-phospholipid modulator of the Edg-1 receptor sufficient to modulate the Edg-1 receptor mediated biological activity.

**III. Responses to the Objections**

***Claim 1, the term "Edg" is not spelled out***

Claim 1 is objected to because the term "Edg-1" is not allegedly spelled out when first used in a claim. Applicants respond with a combination of an amendment and traversal.

For the purpose of expediting prosecution only, Applicants have amended claim 1 to recite "endothelial gene differentiation-1("Edg-1")". Therefore, Applicants respectfully request that this objection be obviated.

***Claim 20, recitation of non-elected subject matter***

Claim 20 is objected to because the claim allegedly contains non-elected subject matter. Applicants respond with a combination of amendments and traversal.

For the purpose of expediting prosecution, Applicants have incorporated the elected subject matter (vasoconstriction) into claims 1 and 2. Applicants have canceled claim 20. Consequently, this objection is now moot. Therefore, Applicants respectfully request that this objection be obviated.

***Claim 27, the terms "VEGF" and "cAMP" are not spelled out***

Claim 27 is objected to because the terms "VEGF" and "cAMP" is not spelled out when first used in a claim. Applicants respond with a combination of an amendment and traversal.

Applicants point out that the terms "VEGF" and "cAMP" are in claim 20, not claim 27. As discussed above, Applicants have canceled claim 20. Thus, the objection is now moot. Therefore, Applicants respectfully request that this objection be obviated.

***Claims 33-37, recitation of non-elected species***

Claims 33-37 are objected to for recitation of non-elected species. Applicants respond with a combination of amendments and traversal.

For the purpose of expediting prosecution, Applicants have deleted claim 33. Applicants have amended claims 34-37 to recite the elected species. Therefore, Applicants respectfully request that this objection be obviated.

**IV. Responses to the Rejections**

***Under 35 U.S.C. § 112, second paragraph, claims 1 and 2 for biological activity and non-phospholipid modulator***

Claims 1 and 2 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that the mediated biological

activity is indefinite. The Examiner also states that the phrase “what the modulator is not” is indefinite. Applicants respond with a combination of amendments and traversal.

Without acknowledging the propriety of the indefiniteness rejection and for the purpose of expediting prosecution, Applicants have amended claims 1 and 2 to recite the biological activity is vasoconstriction. Similarly, Applicants have also amended claims 1 and 2 to recite a non-phospholipid modulator.

Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

***Under 35 U.S.C. § 112, second paragraph, opposite directions***

Claims 3 and 4 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that the claims operate in distinct opposite directions. Applicants respond with a combination of an amendment and traversal.

Without acknowledging the propriety of the indefiniteness rejection and for the purpose of expediting prosecution, Applicants have canceled claim 3. Applicants expressly reserve the right to pursue the canceled claim in another application.

Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

***Under 35 U.S.C. § 112, second paragraph, “other Edg receptors”***

Claims 5-8 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that the term “other Edg receptors” is indefinite. Applicants respond with a combination of amendments and traversal.

Without acknowledging the propriety of the indefiniteness rejection and for the purpose of expediting prosecution, Applicants have amended claims 5-8, changing “other Edg receptors” to “Edg-2, Edg-4 and Edg-7”. Support for the recitation can be found throughout the specification, such as Table 2.

Therefore, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

***Under 35 U.S.C. § 112, second paragraph, “at least about”***

Claims 5-8 are rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states that claims reciting the phrase “at least about” are indefinite. Applicants traverse.

Applicants submit that claims reciting “at least about” are definite. The MPEP cites a narrow court case in which claims reciting the phrase “at least about” may be held invalid for indefiniteness. See MPEP 2173.05(b)(A) Courts have held that claims reciting “at least about” were invalid for indefiniteness when there was close prior art and there was nothing in the specification, prosecution history or the prior art to provide any indication as to what range of specific activity is covered by the term “about”. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991).

In the instant case, there was no close prior art cited that could read on Applicants’ ranges for inhibitory activity for a modulator using a compound of Formula (Ia). Since this element of the above-referenced test is missing, claims reciting the phrase “at least about” are therefore definite.

Therefore, Applicants respectfully request that this rejection be withdrawn.

***Under 35 U.S.C. § 112, second paragraph, “between about” and femtomolar***

Claim 21 is rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Specifically, the Examiner states the claim reciting the phrase “between about” is indefinite. Furthermore, the Examiner states that “fM” is unclear. Applicants traverse.

Applicants submit that claim 21 reciting the phrase “between about” is definite for the reasons discussed above in the “at least about” section. Furthermore, Applicants have amended claim 21 to clarify that the term “fM” is femtomolar. Support for this recitation can be found on paragraph 0141 on page 22 of the specification.

Therefore, Applicants respectfully request that these rejections be withdrawn.

***Under 35 U.S.C. § 112, first paragraph, prevention and all receptor mediated biological activity***

Claims 20 and 33-36 are rejected under 35 U.S.C. § 112, first paragraph because the specification is allegedly not enabling for preventing all types of vasoconstriction and all receptor-mediated biological activities. Applicants respond with a combination of amendment and traversal.

As discussed above, vasoconstriction from claim 20 is incorporated into claims 1 and 2. Claim 20 is now canceled. Since claim 20 is canceled, this rejection is now moot. Therefore, Applicants request that this rejection be withdrawn.

Without acknowledging the propriety of the enablement rejection and for the purpose of expediting prosecution, Applicants have deleted the terms “preventing” and “prevention” from claims 33-36. Applicants expressly reserve the right to pursue the deleted subject matter in a later application.

The Examiner admits from the outset that the specification is enabling for treating vasoconstriction. See the last line on page 4 of the Office Action. In addition to the Examiner’s admission, Applicants point that the specification contains numerous references to treating vasoconstriction in a subject.

The specification teaches methods for using Edg-1 modulators (i.e., agonists or antagonists) in treating or reducing the risk of developing vasoconstriction in cerebral arteries. See page 3, paragraph 0009; page 18, paragraph 0110; page 35, paragraph 0174; and page 36, paragraph 0176. Furthermore, the specification teaches that activation of Edg-1 receptors by using an Edg-1 agonist can result in treating vasoconstriction. See page 3, paragraph 0009; page 18, paragraph 0110; page 35, paragraph 0174; and page 36, paragraph 0176. Therefore, the specification is enabling with respect to treating vasoconstriction.

Applicants respectfully request that this rejection be withdrawn.

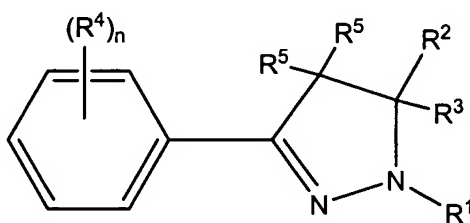
***Under 35 U.S.C. § 102(b)***

To maintain a *prima facie* case of anticipation, the Examiner must demonstrate that each and every element as set forth in the claim is either expressly found or is inherently described in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the ...claim. See MPEP § 2131. Applicants submit that each element of the claims now pending have not been identified in the art presently of record. Therefore, Applicants traverse.

*Over Waeber*

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Waeber *et al.* (U.S. Pat. Pub. No. 2001/0041688 A1) ("Waeber"). Waeber is cited by the Examiner for disclosing a method of modulating an Edg-1 receptor. Furthermore, the Examiner states that Waeber discloses one of the modulators is N,N-dimethyl sphingosine which is a non-phospholipid. Moreover, the Examiner states that Waeber discloses a screening method in which a cell is contacted with N,N-dimethyl sphingosine. The Examiner also states that Waeber discloses that the modulator can be an agonist or an antagonist. However, Applicants submit that this reference is missing at least one element which is present in the claims currently pending.

Applicants have amended claims 1 and 2 to recite a modulator is a compound of Formula (Ia):



(Ia)

In contrast, Waeber fails to teach Formula (Ia) in its disclosure. Since Waeber fails to teach Formula (Ia) and this is an element of Applicants' claimed invention, an anticipation rejection cannot be maintained.

Therefore, Applicants respectfully request that this rejection be withdrawn.

Over Au Young

Claims 1-4 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Au Young *et al.* (U.S. Pat. No. 5,912,144) ("Au Young"). Au-Young is cited by the Examiner for disclosing a method of modulating an Edg-1 receptor wherein the Edg-1 receptor is an antisense molecule and a non-phospholipid. Furthermore, the Examiner states that Au-Young also discloses that the modulator can be an agonist or an antagonist. However, Applicants submit that this reference is missing at least two elements which are present in the claims currently pending.

First, Applicants have amended claims 1 and 2 to recite that a modulator is a compound of Formula (Ia). In contrast, Au Young fails to teach a modulator is a compound of Formula (Ia). Since Au Young fails to teach Formula (Ia) and this is an element of Applicants' claimed invention, an anticipation rejection cannot be maintained.

Second, Applicants have amended claims 1 and 2 to recite that the biological activity is vasoconstriction. In contrast, Au Young fails to teach or even suggest that an Edg-1 receptor may be involved in mediating vasoconstriction. Since Au Young fails to teach mediating vasoconstriction, and this is an element of Applicants' claimed invention, an anticipation rejection cannot be maintained.

Therefore, Applicants respectfully request that this rejection be withdrawn.

Under 35 U.S.C. § 103(a)

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate that (1) the references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir.1991). For the reasons described below, the cited references fail to establish a *prima facie* case of obviousness and Applicants therefore traverse.

Over Waeber in view of Au-Young, Waeber in view of Liao

Claims 1-17 and 20-26 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Waeber in view of Au-Young and Waeber in view of Liao *et al.* (U.S. Pat. Pub. 2002/0155512 A1). Waeber is cited by the Examiner for disclosing a method of modulating an

Edg-1 receptor wherein the modulator is N-N-dimethyl sphingosine. The Examiner further states that Waeber discloses that the modulator is a non-phospholipid. The Examiner also states that Waeber discloses the modulator can be an agonist or an antagonist. The Examiner also states that Waeber discloses vasoconstriction as a biological activity. Au-Young is cited by the Examiner for disclosing a method of modulating an Edg-1 receptor wherein the modulator is an antisense molecule. The Examiner further states that Au-Young discloses the modulator is a non-phospholipid. The Examiner further states that Au-Young discloses the modulator can be an agonist or an antagonist. Liao is cited by the Examiner for disclosing the modulator of Edg-1 is 2-amino-2(2-[4-octylphenyl]ethyl)-1,3-propanediol hydrochloride whose molecular weight is less than 750 daltons. Additionally, the Examiner states that Liao discloses that the binding constant is at least 1  $\mu$ M. However, Applicants submit that none of the references discloses Applicants' Formula (Ia).

As a preliminary matter, Applicants remind the Examiner that claim 13 was withdrawn as being directed to non-elected subject matter. Claims 14-17, which are dependent on claim 13, were examined on the merits. The Examiner has rejected claims 13-17 as allegedly being obvious over Waeber in view of Au-Young. Due to the fact that claims 14-17 are dependent on claim 13, Applicants have canceled claims 14-17. Therefore, Applicants respectfully request that the rejection of claims 13-17 be withdrawn.

*(1) Waeber, Au-Young and Liao fail to teach all of the elements*

Waeber, Au-Young and Liao all fail to teach a modulator is a compound of Formula (Ia). Furthermore, Au-Young fails to teach or suggest using Formula (Ia) in mediating vasoconstriction. Additionally, both Waeber and Au-Young fail to teach specific ranges of inhibition activity of a compound having Formula (Ia).

Since Waeber, Au-Young and Liao are missing at least one element of Applicants' invention, Waeber, Au-Young and Liao fail to teach all of the claimed elements of Applicants' invention. Therefore, a *prima facie* obviousness rejection cannot be maintained.

*(2) There is no suggestion or motivation to modify teachings of the references*

Waeber, Au-Young and Liao also fail to disclose or suggest that a modulator is a compound of Formula (Ia). Additionally, Au-Young fails to suggest using Formula (Ia) in



mediating vasoconstriction. Furthermore, Waeber and Au-Young both fail to suggest specific ranges for inhibition activity of a compound having Formula (Ia). Therefore, a *prima facie* obviousness rejection cannot be maintained.

(3) *Waeber, Au-Young and Liao do not provide a reasonable expectation of success*

Waeber, Au-Young and Liao also fail to provide a reasonable expectation of success in performing the Applicants' invention. As mentioned earlier, there is nothing in the references that suggests a modulator is a compound of Formula (Ia). Additionally, Au-Young fails to suggest using Formula (Ia) in mediating vasoconstriction. Moreover, Waeber and Au-Young fail to suggest a specific range for inhibition activity of a compound of Formula (Ia). Furthermore, Waeber, Au-Young and Liao offer no guidance to one of ordinary skill in the art regarding a modulator is a compound of Formula (Ia). Accordingly, Waeber, Au-Young and Liao do not create a reasonable expectation of success that their method can be successfully used for the purpose of Applicants' invention. Therefore, a *prima facie* obviousness rejection cannot be maintained.

Because Waeber, Au-Young and Liao fail to teach all the claimed elements, do not contain a suggestion or motivation to modify the reference teachings, and do not provide a reasonable expectation of success, a *prima facie* case of obviousness cannot be set forth. Thus, Applicants respectfully request withdrawal of the rejection.

Over Waeber in view of Chen

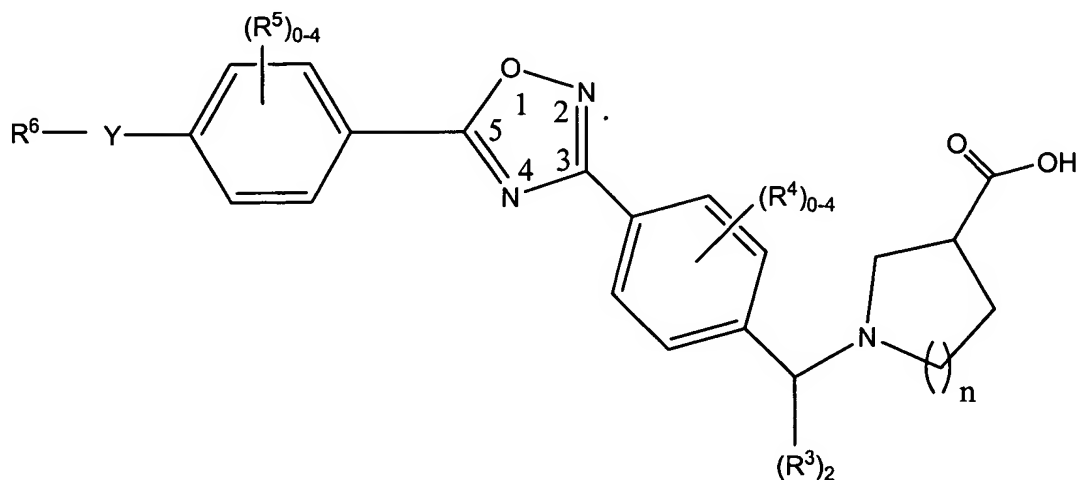
Claims 28, 33-37 and 42 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Waeber in view of Chen *et al.* (U.S. Pat. Pub. No. 2005/0245575 A1)("Chen"). Waeber is cited by the Examiner for disclosing a method of treating vasoconstriction by administering a therapeutic amount of a compound. Chen is cited by the Examiner for disclosing that the core structure of a compound disclosed in paragraph 0013 reads on Applicants' Formula (I). However, Applicants have amended claims 34-36 to recite the modulator is a compound of Formula (Ia). Applicants submit that the core structure in Chen is different from Applicants' Formula (Ia).

*(1) Waeber and Chen fail to teach all of the elements*

As discussed earlier, Waeber fails to teach a modulator is a compound of Formula (Ia). Moreover, both Waeber and Chen fail to teach specific ranges of inhibition activity for a compound of Formula (Ia). Additionally, Chen fails to teach or suggest mediating vasoconstriction using Formula (Ia).

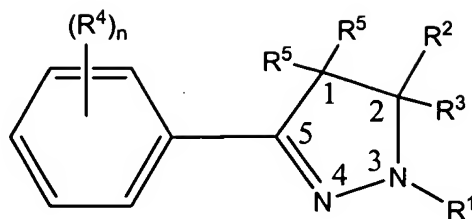
Furthermore, the compound disclosed in Chen is different from Applicants' Formula (Ia). Chen discloses an oxadiazole ring in which there are two double bonds in the ring, an oxygen atom at position 1, a nitrogen atom at position 2 and a carbon atom at position 3. In contrast, Applicants recite a pyrazoline ring in which there is one double bond in the ring, a carbon atom at position 1, a carbon atom at position 2 and a nitrogen atom at position 3. To further illustrate this point, Applicants have drawn out both compounds.

Chen discloses the following compound:



Applicants have inserted position numbers to the oxadiazole ring to assist with the discussion.

In contrast, Applicants recite a modulator which is a compound of Formula (Ia):



(Ia)

Applicants have also inserted position numbers to the pyrazoline ring to assist with the discussion.

As clearly illustrated above, Chen's oxadiazole ring is completely different from Applicants' pyrazoline ring. Applicants further submit that its structure is not a homolog of Chen's structure because Chen's oxadiazole ring is clearly different from Applicants' pyrazole ring.

Since Waeber and Chen do not disclose a modulator is a compound of Formula (Ia) and this is an element of Applicants' claimed invention, Waeber and Chen fail to teach all of the claimed elements of Applicants' invention. Therefore, a *prima facie* obviousness rejection cannot be maintained.

*(2) There is no suggestion or motivation to modify teachings of the references*

As discussed above, Waeber and Chen fail to disclose or suggest a modulator is a compound of Formula (Ia). Additionally, Waeber and Chen fail to disclose or suggest specific ranges of inhibitory activity for a compound having Formula (Ia). Moreover, Chen also fails to suggest using Formula (Ia) for mediating vasoconstriction. Therefore, a *prima facie* obviousness rejection cannot be maintained.

*(3) Waeber and Chen do not provide a reasonable expectation of success*

Waeber and Chen also fail to provide a reasonable expectation of success in performing the Applicants' invention. As mentioned earlier, there is nothing in the references that suggests a modulator is a compound of Formula (Ia). Additionally, Waeber and Chen fail to disclose or suggest specific ranges of inhibitory activity for a compound having Formula (Ia). Moreover, Chen fails to suggest using Formula (Ia) for mediating vasoconstriction. Furthermore, Waeber and Chen offer no guidance to one of ordinary skill in the art regarding a

modulator is a compound of Formula (Ia). Accordingly, Waeber and Chen do not create a reasonable expectation of success that their method can be successfully used for the purpose of Applicants' invention. Therefore, a *prima facie* obviousness rejection cannot be maintained.

Because Waeber and Chen fail to teach all of the claimed elements, do not contain a suggestion or motivation to modify the reference teachings, and do not provide a reasonable expectation of success, a *prima facie* case of obviousness cannot be set forth. Thus, Applicants respectfully request withdrawal of the rejection.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1000.

Respectfully submitted,



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